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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/824,787	04/04/2001	Maurice Zauderer	1821.0040001/EKS/TJS	2970
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STERNE, KESSLER, GOLDSTEIN & FOX PLLC 1100 NEW YORK AVENUE, N.W., SUITE 600 WASHINGTON, DC 20005-3934			EXAMINER	
			HARRIS, ALANA M	
		ART UNIT	PAPER NUMBER	18
		1642		

DATE MAILED: 02/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/824,787	ZAUDERER ET AL.
	Examiner	Art Unit
	Alana M. Harris, Ph.D.	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 22 November 2002.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-37 is/are pending in the application.
- 4a) Of the above claim(s) 1-10,13-15,17-22,24-27 and 30-37 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 11,12,16,23,25,28 and 29 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) The translation of the foreign language provisional application has been received.
- 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|---|--|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ . |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>15</u> . | 6) <input type="checkbox"/> Other: _____ . |

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group II (claims 11, 12, 16, 23, 25, 28 and 29) in Paper No. 14, received July 22, 2002 is acknowledged. The traversal is on the ground(s) that the search and examination at a minimum of Group I together with Groups VII and XI and Group II together with Groups VII, IX and X would not impose a serious burden on the examiner. This is not found persuasive because the elected Group II is drawn to a product, which is functionally distinct from the product of Group I. Further, method Groups VI, IX and X involve different method steps, which require additional searching.

As to the question of burden of search, the claims of Groups I, II, VII, IX, XI and X are classified differently, necessitating different searches in the U.S. Patent Office. Further, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not co-extensive and is much more important in evaluating the burden of search. Clearly different searches and issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is adhered to.

The requirement is therefore made FINAL.

However, the policies set forth in the Commissioner's Notice of February 28, 1996 published on March 26, 1996 at 1184 O.G. 86 will be followed. Method claims limited to the scope of the allowable product claims will be rejoined and examined at the time the product claims are indicated as being allowable.

Art. Unit: 1642

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-37 are pending.

Claims 1-10, 13-15, 17-22, 24-27 and 30-37, drawn to non-elected inventions are withdrawn from examination.

Claims 11, 12, 16, 23, 25, 28 and 29 are examined on the merits.

Information Disclosure Statement

3. The information disclosure statement filed October 16, 2002 as Paper No. 15 has been considered by the Examiner. However, copies of all documents "lined through" were not found in the file and were not considered by the Examiner. Applicant is invited to provide replacement copies.

Claim Objections

4. Claims 11, 23 and 25 are objected to because of the following informalities:

- claims 11 and 25 are identical; and
- claim 23 depends upon a non-elected claim. For examination purposes the limitations of claim 22 will be read into examined claim 23.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 11, 12, 25, 28 and 29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 11 and 25 broadly claim an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence selected from the group consisting of:

- (a) a polypeptide fragment of SEQ ID NO: 2;
- (b) a polypeptide fragment of SEQ ID NO: 2 having biological activity;
- (c) a polypeptide domain of SEQ ID NO: 2;
- (d) a polypeptide epitope of SEQ ID NO: 2;
- (e) a mature form of a secreted form of SEQ ID NO: 2;
- (f) a full length secreted form of SEQ ID NO: 2;
- (g) a variant of SEQ ID NO: 2;
- (h) an allelic variant of SEQ ID NO: 2; or
- (i) a species homologue of the SEQ ID NO: 2. The written description in this instant case only sets forth polypeptide, SEQ ID NO: 2. The written description is not commensurate in scope with the claim drawn to the variant and mutated polypeptides embodied by a sequence of 95% homology to SEQ ID NO: 4 and claims encompassing the variant polypeptides.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought,

he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 115).

With the exception of SEQ ID NO: 2, the skilled artisan cannot envision the detailed structure of the encompassed polypeptides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The polypeptide itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

Furthermore, In *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA..." requires a precise

Art Unit: 1642

definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

At the time the application was filed Applicants only had possession of SEQ ID NO: 2 and not polypeptides that share 95% sequence identity with SEQ ID NO:2. The specification does not evidence the possession of all the possible variant and mutant polypeptides that could be or may not be capable of exhibiting activities of a wild type C35 polypeptide. There is insufficient to support the generic claims as provided by the Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

The full breadth of the claims do not meet the written description provision of 35 U.S.C. 112, first paragraph.

7. Claim 28 and 29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, does not reasonably provide enablement commensurate with the scope of the claimed invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Claim 28 is drawn to a pharmaceutical composition comprising SEQ ID NO: 2, fragments, variants, allelic variants and species homologues of the said sequence for the use in therapy. The specification while being enabling for a composition comprising SEQ ID NO:2 and a pharmaceutically acceptable carrier, does not reasonably provide enablement for a "pharmaceutical composition" comprising these same components.

Claims drawn to “pharmaceutical compositions” are broadly interpreted to read on compositions effective for use as *in vivo* therapeutics. In the absence of an established role of these proteins in human breast and bladder carcinoma diseases it is impossible to predict what if any therapeutic effect the administration of these molecules would have for the treatment of cancers. Applicants have not provided any experimental data that evidences the administration of fragments and variants of SEQ ID NO: 2, as well as SEQ ID NO: 2 itself term for osteoprotegerin-like. However, there is no data or established precedent presented that would lead one of skill in the art to believe that the C35 polypeptides and fragments and variants, thereof would be able to induce antibody and cell-mediated immunity against target cells, such as tumor cells.

The selection and development of such therapeutics is art known to be highly unpredictable. The specification exemplifies no examples of the effective use of the C35 polypeptide identified as SEQ ID NO: 2 as a therapeutic pharmacological agent and no such uses are art known. This reasonably conjures the question as to how selective the use of the claimed composition clearly is or would be. Therefore, due to the unpredictability of therapeutics and the absence of any evidence concerning the effectiveness of the claimed pharmaceutical composition as a pharmacological agent, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use with a reasonable expectation of success, the invention commensurate in scope with this claim. There is no guidance as to how the instant molecules can be employed as therapeutic nor a basis to predict their efficacy in any therapy. Additionally, it would require undue experimentation of one

skilled in the art to apply a method of treatment to a human based on the teachings of a method of treating a non-human animal. The applicant is advised to amend the claim to delete the recitation of "pharmaceutical" and specify the type of therapy designated for the use of a composition.

8. Claims 11, 12, 16, 23, 25, 28 and 29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, does not reasonably provide enablement commensurate with the scope of the claimed invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Claim 11, 12 and 25 is broadly drawn to an isolated polypeptide comprising an amino acid at least 95% identical to SEQ ID NO: 2, as well as variants which contain enumerable deletions and substitutions. The specification while being enabling for the polypeptide having the amino acid sequence of SEQ ID NO:2, does not reasonably provide enablement for variants that have at least 95% sequence identity or variants that contain deletions from either or both the C-terminus or N-terminus. There is no guidance as to how to make these divergent sequences. The products of these 95% sequence identical molecules may possess function that is not commensurate with the functions of the native protein. The 95% sequence identical amino acids may not maintain the activities proposed in the specification. It would seem that specific function(s) would be required to make the encoded protein useful for the applications disclosed in the specification, such as for treating breast and bladder carcinomas and in

Art Unit: 1642

diagnostic applications. Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar activity requires a knowledge of and guidance with regard to which amino acid or acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved and detailed knowledge of the ways in which the protein's structure relates to its function. The specification provides essentially no guidance as to which of the infinite possible choices is likely to be successful. The true fact of the state of the art in peptide chemistry is expressed succinctly in the accompanying Lazar article (*Molecular and Cellular Biology* 8(3): 1247-1252, March 1988). This article presents data that substantiates the fact that the introduction of mutations in an amino acid sequence will yield products with different biological activity from the wild type protein.

From the discussion above, it is clear that the predictability of changes to the amino acid sequence is practically nil as far as biological activities are concerned. The specification fails to provide sufficient guidance to enable one of ordinary skill in the art to make and use the claimed amino acids in a manner reasonably correlated with the broad scope of the claims. Without such guidance, the changes which must be made in the nucleic sequence that encodes the variants of SEQ ID NO: 2, which results in amino acid sequences with 95% identity and/or undefined substitutions is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue.

Art Unit: 1642

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 11, 12, 23 and 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 11 and 25 are vague and indefinite in the recitations "polypeptide domain" and "polypeptide epitope". It is not clear if the entire amino acid sequence of SEQ ID NO: 2 is regarded as the domain or epitope or specific amino acid residues are regarded. Accordingly, the metes and the bounds cannot be determined.

b. Claim 23 is vague and indefinite in the term "product". It is not clear what product is being referenced. Furthermore, the term lacks proper antecedent bases.

Correction is required.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in-

(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or

(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

12. Claims 11, 12, 16, 23, 25, 28 and 29 rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent number 5,856,131 (filed February 24, 1997). Sequence 3 of U.S. patent #5,856,131 discloses an isolated polypeptide comprising an amino acid sequence at least 95% identical to a polypeptide fragment having biological activity, a polypeptide domain, a polypeptide epitope, a variant, an allelic variant and a species homologue of SEQ ID NO: 2, see attached database sheet. The mature form or the full length secreted protein comprises sequential amino acid deletions from both the C-terminus and the N-terminus. Patent '131 also discloses a pharmaceutical composition comprising the isolated polypeptide and an adjuvant in combination with a pharmaceutically acceptable carrier, see column 17, lines 2-10; column 19, line 46-column 22, line 4.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alana M. Harris, Ph.D. whose telephone number is (703) 306-5880. The examiner can normally be reached on 6:30 am to 4:00 pm, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4315 for regular communications and (703) 308-4315 for After Final communications.

Art Unit: 1642

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

ALANA HARRIS
PATENT EXAMINER


Alana M. Harris, Ph.D.
February 7, 2003